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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,787	02/11/2000	Laurent Coen	03495.0187	4369

22852 7590 08/16/2006

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/501,787	COEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 July 1006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *12 July 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-5,8-11,31 and 33-37*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Attachment to Advisory Action

Claims 1-5, 8, 11, 31, 34, 36 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as set forth previously and reiterated below.

U.S. Patent No: 5780024 discloses an in vivo method for delivery (e.g. intramuscular, see col 4) of a composition (SOD:Tet451), comprising a the tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see col 1). Further, U.S. Patent No: 5780024 disclosed that the method can be used in the treatment of neurodegenerative diseases of the CNS (see col 1 for example).

U.S. Patent No: 5780024 discloses that the tetanus toxin C fragment used in the method of delivery can include additional amino acids, see col 6, as a matter of routine optimization of operating perimeters; yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment nor that the there should be exactly 11 (claim 37). U.S. Patent No: 5780024 disclose embodiments having 2 or 8 additional amino acids (col 6) and indicate that more or less are encompassed by the invention, and can be added, particularly as a matter of convenience in the cloning process, e.g. col 6, lines 37-40. However, Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-

fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the invention disclosed in U.S. Patent No: 5780024 The motivation to do so was provided by both U.S. Patent No: 5780024, wherein it was taught that additional amino acids of the B-fragment may be added to the C-fragment as a matter of routine optimization, and Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the invention of U.S. Patent No: 5780024, e.g. see col 1, lines 64-col 2 line 9 of U.S. Patent No: 5780024 .

Applicant's arguments essentially evolve from two assertions: 1) that the basis of the rejection is an "obvious to try" standard, and 2) that one of ordinary skill in the art would not expect the fusion protein to undergo transynaptic transport. These arguments has been fully considered but not deemed persuasive.

The basis of the rejection is a simple routine optimization of operating parameters as specifically suggested by Halpern. who specifically teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, as discussed above. This is a specific teaching and not a situation where the "prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" as Applicant asserts.

Second, Applicant argues that the Office has not explained the basis for the asserted expectation that the fusion protein would be capable of transynaptic transport. This argument has been fully considered but not deemed persuasive. The examiner has repeatedly pointed to col 4, lines 34-44 of the '024 patent, wherein it is specifically taught that the fusion peptide is expected to undergo "transynaptic transfer between neurons".

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to claims 1-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990, as set forth previously.

Applicant's arguments are essentially addressed above.

Claims 1-5, 8, 11, 31, 33-36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously. Applicant's arguments have been addressed above.

Claims 1-5 8, 11, 31, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as set forth previously and reiterated below:

Francis et al. disclose an in vitro method for delivery of a composition (SOD:Tet451), comprising a tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein, absent evidence to the contrary, the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see page 15434). Francis et al. did not use the method for in vivo delivery, however they proposed to do so (see the Abstract, for example). Further, Francis et al disclosed that the method could be used in the treatment of neurodegenerative diseases of the CNS (15434 see col 1 for example). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to with reasonable expectation of success to use the in vitro method of delivery disclosed by Francis et al. for in vivo delivery, as required by the instant claims. The motivation to do so was provided by Francis et al. who state the tetanus toxin has a well documented capacity for neuronal binding and internalization. In particular when administered systemically or intramuscularly to animals, the toxin is taken up selectively by motor neurons in the brain stem and spinal chord. The C-fragment retains these properties without the toxic domain (see 15434 see col 1). Further, Francis et al. hypothesize that their disclosed fusion protein could increase the delivery of the SOD-1 protein to the central

nervous system in general and motor neurons in particular, potentially providing effective enzyme therapy to neurons (see 15434 see col 1).

Francis et al. disclose that it is the C-fragment of tetanus that provides for neuronal binding and internalization without toxicity, yet Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment. Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the method taught and proposed by Francis et al. The motivation to do so was provided by Halpern et al. who teach that additional amino acids of the B-fragment may

enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the method taught and suggested by Francis et al..

Applicant's arguments regarding Halpern have been essentially addressed above. Applicant further argues that neither Halpern or Francis et al. disclose in vivo transynaptic transport and that one would be surprised to obtain the effects Applicants have discovered. This argument has been fully considered but not deemed persuasive. Referring to the uptake of the fusion protein by motor neurons, at page 15441, col 1, last sentence of the first full paragraph, Frances et al. teach that through this pathway, the hybrid protein could access other central nervous system neurons as well, given the ability of TTC to undergo retrograde trans-synaptic transfer". Thus, Frances et al. specifically assert that hybrid protein is capable of transynaptic transport. Applicant has provided no reasons as to why one of ordinary skill in the art would not believe the teachings of Frances et al.

Claims 8, 11, 31, 33, 35, 36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously and reiterated above.

Applicant's elected species of SMN (claim 8) is not taught by either Francis et al. or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of

ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern et al. and by Francis et al., as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments have been addressed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

August 11, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER